REMARKS

Claims 61-88 were pending in the instant application. No claims have been amended, added, or cancelled. For the Examiner's convenience, a copy of the pending claims are submitted herewith as Appendix A.

The specification has been amended to remove the blank lines and insert the ATCC Deposit Accession Number. The title has been amended to more accurately describe the claimed invention. No new matter has been added.

Rejection of Claims 61-88 Under 35 U.S.C. §101

The rejection of claims 61-88 under 35 U.S.C. §101 has been maintained because, according to the Examiner, "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Applicant respectfully traverses the foregoing rejections, as detailed in the prior responses. Applicant has identified the various portions of the specification that are relied upon to show that the claimed invention meets the requirements of §101, and those arguments are expressly incorporated herein by reference.

It is Applicant's position that based on the guidelines set forth in the *Revised Interim Utility Guidelines Training Materials* (in particular, Example 10 at pages 53-54) the present invention has a specific and substantial utility which is credible. The hypothetical scenario set forth in Example 10 of the Guidelines is a specification disclosing a novel protein which demonstrates a high level of homology to a DNA ligase. In particular, the Guidelines provide that "[b]ased on the sequence homologies, the specification asserts that SEQ ID NO:2 (the claimed sequence at issue) encodes a DNA ligase." The United States Patent and Trademark Office provides the following guidance in assessing the utility of the invention described above, "[b]ased upon applicant's disclosure and the results of the PTO search, there is no reason to doubt the assertion that SEQ ID NO:2 encodes a DNA ligase. Further, ***DNA ligases have a well-established use in the molecular biology art based on this class of protein's ability to ligate DNA***." The conclusion in Example 10, based on the foregoing analysis, is that the novel ligase molecules of the hypothetical invention satisfy the requirements of 35 U.S.C. §101.

Similar to Example 10 in the *Interim Utility Guidelines*, the present invention is directed to the identification and characterization of four members of the CRSP family, which have a

well-established utility in secreting signaling factor proteins and which play a role in the well-known and well-characterized Wnt-signaling pathway. The pending claims are specifically drawn to CRSP-2 and methods of using same. ***The instant application teaches that CRSP-2 and members of the CRSP family are novel secreted soluble signaling proteins*** (page 1, lines 37-38 of the specification) ***involved in the modulation of development and differentiation*** (page 1, line 15-16; page 1, lines 29-34; and page 2, lines 1-3 of the specification). Applicant is not relying on subsequent research as suggested at page 3 of the Office Action. Rather, Applicant respectfully submits that the foregoing teachings, which support a well-established utility, have been *confirmed* by post-filing evidence.

The Examiner is of the opinion that "the specification is silent with respect to the specific biological functions of the protein" (page 4 of the Office Action). Contrary to the Examiner's assertions, Applicant respectfully submits that the instant specification teaches multiple biological activities of CRSP-2. Indeed, Applicant teaches that "CRSP activity," *i.e.*, the "biological activity" or "functional activity" of CRSP (page 10, lines 33-36 of the specification), includes, for example, "***modulation of cellular signal transduction, either in vitro or in vivo***" (see page 11, lines 23-24 of the specification), "***regulation of gene transcription in a cell involved in development or differentiation, either in vitro or in vivo***" (page 11, lines 24-25 of the specification), and "***regulation of cellular proliferation***" (page 11, line 31 of the specification).

Similar to Example 10, Applicant's specification asserts that the molecules of the present invention belong to the CRSP family based upon sequence homology to members of this family. In particular, Applicant's specification teaches that the amino acid sequence of human CRSP-2 (SEQ ID NO:5) contains many significant domains and sites which further confirm Applicant's asserted utility. Specifically, the CRSP-2 proteins of the present invention contain hydrophobic signal peptides and strongly conserved cysteine residues, with potential for disulfide cross-linking (page 8, lines 3-5 and 24-28 of the specification). In addition, a signal sequence at about amino acids 1-19 of SEQ ID NO:5 have been identified in CRSP-2, further confirming Applicant's teachings that CRSP-2 is a secreted protein (page 9, lines 27-29 of the specification).

The Examiner also states, "[w]ith respect to Wnt-signaling, the passage recited by Applicant makes no mention of the ability of CRSP-2 to inhibit Wnt-signaling." Applicant traverses this rejection and respectfully submits that the teachings in the instant specification are more than sufficient for establishing a well-established utility based upon the *Interim Utility*

Guidelines. Applicant respectfully submits that while the Examiner has maintained this rejection in the present Office Action, the Examiner has not addressed the responsive argument presented by the Applicant in the previous Amendment and Response filed on March 17, 2003. In summary, the instant specification describes that Wnt proteins are "recognized as one of the major families of developmentally important signaling molecules..." and cites a journal reference, which is incorporated by reference (see, page 1, lines 25-28 and page 69, lines 16-19 of the specification). Applicant further discloses that CRSP activity may be indirect or due to a complex formation with a second soluble CRSP binding partner, wherein the CRSP binding partner is a non-CRSP protein molecule (page 11, lines 10-20 of the specification). ***However, the disclosure of the precise mechanism by which CRSP-2 inhibits Wnt signaling should not be a prerequisite to the patentability of the present invention***. In particular, knowledge of the Wnt mechanism of inhibition has no bearing on performing a method for identifying a compound that modulates the activity of a CRSP protein and making and using the CRSP proteins of the invention. Accordingly, Applicant contends that a skilled artisan would be able to practice the claimed invention, based on the teachings in Applicant's specification and the knowledge of one skilled in the art.

The Examiner asserts that the specification does not support the teachings of Krupnik *et al.* and Mao *et al.* Furthermore, the Examiner is of the opinion that "with regard to the teachings of Krupnik *et al.* and Mao *et al.* references, it is still unclear what specific function(s) hDkk4 performs in humans. While hDkk4 can apparently inhibit Wnt-signaling in an experimental system (*Xenopus* embryos), it is unclear what function this protein performs in humans." Applicant respectfully traverses the foregoing rejection. To begin with, the present specification defines the exact CRSP-2 activity that is confirmed by post-filing evidence and described in the references. Applicants respectfully further submit that animal models are routinely used in the art as indicators of the effects in humans. As the Examiner is aware, the standard for fulfilling the utility requirement of 35 U.S.C. §101 and the enablement requirement of 35 U.S.C. §112, first paragraph, is not, for example, evidence of a human phase II clinical study, but rather, Applicant must demonstrate that Applicant's invention has a well-established utility and that one of ordinary skill in the art could make and use the invention without undue experimentation. Furthermore, Applicant asserts that enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted, if routine. See, *In re Wands*, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988). Based on

the teachings of the specification and the state of the art at the time the application was filed, Applicant submits that one skilled in the art would be able to make and use the claimed methods without undue experimentation.

In view of the foregoing, ***Applicant submits that, similar to DNA ligases, the CRSP-2 molecules of the present invention have a well-established use in the art as secreted soluble signaling proteins involved in modulation of development and differentiation***. It is evident that Applicant's invention has a well-established utility that would have been readily apparent to one of skill in the art at the time of the invention. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection under 35 U.S.C. §101.

Rejection of Claims 61-88 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 61-88 under 35 U.S.C. §112, first paragraph. According to the Examiner, "since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Applicant respectfully traverses the foregoing rejection on the basis that Applicant's specification discloses sufficient guidance as to how one of skill in the art would use the claimed invention. As indicated above, Applicant has identified that the CRSP-2 molecules of the present invention are secreted soluble proteins having a well-established utility: the modulation of development and differentiation. Specifically, molecules of the CRSP family have been shown to be secreted signaling factor proteins. Moreover, Applicant's specification discloses ample guidance as to how one of skill in the art would use the claimed invention and the compounds identified using the claimed invention (see, for example, the screening assays, the diagnostic assays, the prognostic assays, and the methods of treatment, *e.g.*, therapeutic and prophylactic, taught by Applicant at page 47, line 18 through page 67, line 9 of the specification). Thus, one of ordinary skill in the art reading the foregoing teachings in Applicant's specification would have been able to make and use the claimed invention using only routine experimentation.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the foregoing 35 U.S.C.§112, First Paragraph rejection.

Objections to the Specification

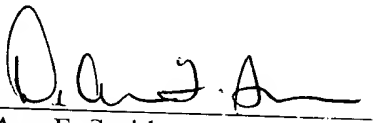
The Examiner has maintained an objection to the specification because of blanks in the specification. The specification has been amended herein, thus, Applicant respectfully requests that the rejection be withdrawn.

CONCLUSION

In view of the foregoing amendments and following remarks, it is respectfully submitted that the application is in condition for allowance. If the Examiner has any questions or believes that a telephone conversation with Applicant's Attorney would be helpful in expediting allowance of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Dated: July 9, 2003

Respectfully submitted,

By 

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